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Reasons for requesting an interferon gamma release test from internal medicine and rheumatology clinics and evaluation of the results

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Ethics Committee Approval
The study was approved by the Afyonkarahisar Health Sciences University Clinical Research Ethics Committee dated 06.01.2023 and numbered 2023/31.
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Tuberculosis is a disease involving many systems, such as the lung, gastrointestinal system, genitourinary system, etc. Detecting this disease in its latency significantly reduces the morbidity and mortality associated with tuberculosis. One of the tests used in latent TB screening is the interferon gamma release test. In rheumatology practices, it is routinely used to screen for latent tuberculosis infections before treatment with biological agents and Janus kinase (JAK) inhibitors, and it can also be used to exclude tuberculosis infection in clinical practice. In our study, we aimed to evaluate the reasons for requesting interferon gamma release tests and the results of this test in patients who requested it.
Methods: Patients admitted to internal medicine and rheumatology outpatient clinics were retrospectively screened within the retrospective cohort study. In total, 364 patients who requested interferon gamma release testing were included in the study. Nine patients with unclear test results were excluded. Laboratory results, demographic data, reasons for requesting the interferon gamma release test, and results were evaluated.
Results: The interferon gamma release test was requested by 355 patients. Of these, 266 patients (74.9%) asked for latent tuberculosis screening before treatment with biological agents and JAK inhibitors. This was followed by patients with peripheral lymphadenopathy-lung nodules, patients with unexplained elevated acute phase reactants, and patients with constitutional symptoms, respectively. Ten out of 107 patients (9.3%) had an active tuberculosis infection, while six out of ten patients (60%) had pulmonary tuberculosis, and four (40%) had extrapulmonary tuberculosis.
Conclusion: The most common reason for requesting the interferon gamma release test in internal medicine and rheumatology clinics was screening for latent tuberculosis before treatment with biologic agents and JAK inhibitors. In internal medicine, it has been observed that this test can also be requested by patients with constitutional symptoms, unexplained elevated acute phase reactants, and a preliminary diagnosis of tuberculosis in order to rule out or strengthen the preliminary diagnosis.

Keywords: interferon gamma release test, tuberculosis, biological agent

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Introduction

Tuberculosis (TB) is an infection caused by the Mycobacterium (M.) complex. This complex includes bacteria such as M. tuberculosis, M. bovis, M. caprae, M. africanum, etc., but it is M. tuberculosis that most commonly causes tuberculosis in humans [1,2]. When the human organism encounters M. tuberculosis, it can completely eliminate the bacterium before infection occurs, or it can become infected and develop into a primary or primary progressive disease. Another possibility is that an infection can develop against this bacterium, but most of the bacteria are eliminated and no clinical symptoms occur. This is called latent tuberculosis infection [3]. Latent infection may remain in the host for years without causing disease or may lead to active infection in the future. In low-incidence populations, tuberculosis is usually caused by activation of latent infection rather than primary progression [4]. When the disease becomes active, it can involve all systems, especially the lungs, and cause significant morbidity or death. Therefore, it is very important to recognize the disease in its latency to prevent mortality and morbidity [5].

Although there is currently no gold standard for diagnosing latent tuberculosis infection, the tuberculin skin test (TST) and interferon gamma release tests (IGST) are used for this purpose. These tests have their advantages and disadvantages [6]. Although there is no clear consensus on which one should be used in screening, the fact that the IGST provides an objective assessment and is more sensitive in populations where BCG vaccinations are common, puts it one step ahead. Positive results of these tests indicate exposure to TB bacilli but not active infection.

Latent TB screening is recommended for the high-risk group rather than the general population [7]. Anti-tumor necrosis factor (TNF) agents and Janus kinase inhibitors (JAK), which are widely used in internal medicine and rheumatology, may increase the risk of developing TB. This risk varies in proportion to the incidence of TB in the particular country or community [8]. Therefore, latent TB screening is routinely performed before anti-TNF treatment. Patients with a positive IGST or TST are given TB prophylaxis if they do not have an active TB infection. In addition to latent TB screening, IGST can also be requested to exclude or support the diagnosis of TB in patients with constitutional symptoms, such as fever, weight loss, night sweats, etc., as well as patients with unexplained acute phase reactant elevation, patients with peripheral-hilar-mediastinal lymphadenopathy (LAP), lung nodules, cavities or masses, especially in internal medicine practices.

In this study, we aimed to evaluate the reasons for requesting IGST and the results of this test in patients admitted to internal medicine and rheumatology polyclinics/clinics who requested IGST.

Materials and methods

Patients who applied to Afyonkarahisar Health Sciences University Faculty of Medicine Internal Medicine and rheumatology polyclinic/clinics from Jan. 10, 2020 to January 10, 2022 were contacted through the hospital electronic file system. Among these patients, those requiring IGST were identified. Patients under the age of 18 older than 85 with a history of active tuberculosis infection, chronic renal failure, a history of omcologic/hematologic malignancy, or immunodeficiency were excluded from the study.

Patients were divided into four groups according to their reasons for requesting IGST.

1) Patients with Constitutive Symptoms: Patients with complaints of fever, weight loss, night sweats, fatigue, etc. were included in this group.
2) Acute Phase Reactant Elevation: Patients with unexplained elevated sedimentation and C-reactive protein (CRP) were included in this group.
3) Those screened for TB before biologic agents and JAK inhibitors.
4) Those with peripheral-hilar-mediastinal LAP, nodules, cavities or masses in the lung.

Demographic data, laboratory values, and IGST results of all patients who requested an IGST and these patient groups were evaluated.

Ethics Committee

For this study, the decision of Afyonkarahisar Health Sciences University Faculty of Medicine Clinical Research Ethics Committee dated June 1, 2023 and numbered 2023/31 was approved.

Statistical Analysis

For statistical evaluation, the SPSS 26.0 (IBM Corp. 2019 IBM SPSS Statistics for Windows, version 26.0. Armonk, NY: IBM Corp.) program was used. Descriptive statistics were given as frequency, percentage, mean and standard deviation. The Kolmogorov-Smirnov test, which is a non-parametric test, was used for data with normal distribution. The Mann-Whitney U test was used for abnormally distributed data and the student's t test was used for normally distributed data for the differences between two continuous variable groups. Data with a *P*-value less than 0.05 were considered statistically significant.

Results

A total of 364 patients who requested an IGST were included in the study. Among these patients, nine were excluded from the study due to IGST uncertainty. Of the 355 patients, 143 (40.3%) were male and 212 (59.7%) were female. The youngest patient was 18 years old and the oldest was 83 years old. The mean age was 46.01 (15.20) years.

The laboratory results of the patients included in the study are shown in Table 1.

Among 355 patients, 107 (30.14%) tested positively on the IGST and 248 (69.85%) had negative results. Active TB was found in ten patients. Sixty percent of patients with active TB had pulmonary TB, while 40% had extrapulmonary TB. The most common reason for requesting IGST was for screening before the use of biological agents and JAK-2 inhibitors in (266 patients; 74.9%). The reasons for requesting IGST, positivity and active/latent status are shown in Table 2.

Among the 80 patients with latent TB positivity before treatment with biologic agents and JAK inhibitors, 38 (47.5%) had previously used biologic therapy and JAK inhibitors. Of these 38 patients, 19 had previously completed INH prophylaxis and 51.42 (44.85) months had elapsed since then. Nineteen patients did not complete INH prophylaxis. Among these 19

patients, one patient on Adalimumab who did not receive INH prophylaxis developed active TB.

Table 1 : Laboratory results of patients for whom IGST was requested

	Minimum	Maximum	Mean	SD
WBC(mcL)	8.85	54600.00	9664.8137	2869.01703
HGB(g/dl)	8.1	18.8	13.337	1.9954
Platelet	21300	691000	299080.56	97012.377
AST(IU/L)	7.0	75.0	18.877	8.7891
ALT(IU/L)	3.0	120.0	19.858	14.2625
Urea (mg/dL)	4.7	143.6	29.736	13.0583
Creatinine (mg/dl)	0.31	78.00	1.1854	5.13457
Sedimentation (mm/h)	1	112	29.94	27.039
CRP (mg/dL)	0.10	294.92	19.9882	35.99428

SD: standard deviation, WBC: white blood cell count, HGB: hemoglobin, AST: aspartate aminotransferase, ALT: alanine aminotransferase, CRP: C-reactive protein

Table 2: Reasons for requesting IGST in the patients participating in the study and results thereof

	Number of IGST requests n (%)	IGST positivity n (%)	Active TB n (%)	Pulmonary TB n (%)	Extra-pulmonary TB n (%)
Patients with constitutional symptoms	14 (3.9)	3 (2.8)	2 (20)	1 (16.6)	1 (25)
Patients with Acute Phase Elevation	34 (9.6)	6 (5.6)	2 (20)	-	2 (50)
Before Biological Agents and JAK 2 Inhibitors	266 (74.9)	80 (74.8)	3 (30)	3 (50)	-
Peripheral LAP, Patients with LAP-Nodules in the Lung	41 (11.5)	18 (16.8)	3 (30)	2 (33.3)	1 (25)
Total	355 (100)	107 (100)	10 (100)	6 (100)	4 (100)

A total of 42 patients (52.5%) were naive to biologic agents and JAK 2 inhibitors. These patients were started on TB prophylaxis and no active infection has developed in their follow-up thus far. The biological agents, duration of the treatment and TB status of IGST positive patients who previously used biological agents and JAK 2 inhibitors are given in Table 3.

While there was a statistically significant difference between WBC, sedimentation, CRP ($P<0.001$**)** among the patient groups who requested IGST (constitutional symptoms, acute phase reactant elevation, pre-biologic agent, peripheral LAP-lung nodule), there was no significant difference between other laboratory findings ($P=0.075$). In the post-hoc analysis, it was determined that this difference was due to the variance between the group for whom IGST was requested due to acute phase reactant elevation and the other groups. (Table 4).

Table 3: Biological agents used, duration and tbc status of IGST positive patients who previously used biologic agents and JAK 2 inhibitor therapy

Biological agent	n (%)	Usage period Month	Completing prophylaxis	Active tb n (%)
Sertolizumab	7 (18.4)	23.28	1	2* (66.6%)
Tofasitinib	1 (2.6)	3	-	-
Tocilizumab	1 (2.6)	24	-	-
Anakinra	2 (5.3)	24	1	-
Adalimumab	11 (28.9)	60.63	8	1 **(33.3%)
Golimumab	5 (13.2)	36	2	-
Quadruple Treatment (Biological Agent+JAK inhibitor)	2 (5.3)	102	2	-
Binary Biologics	6 (15.8)	54.5	3	-
Infliximab	2 (5.3)	36	2	-
Etanercept	1 (2.6)	60	-	-
Total	38 (100)	42.30	19	3 (100)

* In a patient diagnosed with rheumatoid arthritis, IGST was negative before sertolizumab treatment, but IGST was found to be positive again in the 6th month of treatment due to constitutional symptoms and cough complaints, and cavitary lesion was detected on lung tomography. ARB was positive, cultures grew TB bacilli. ** This patient completed INH prophylaxis.

Table 4: Post-Hoc analysis between groups

	Std. Error	*P*-value.
Acute phase reactant elevation/Constitutional symptoms	32.587	<0.001
Acute phase reactant elevation/Pre-Biological agent	18.69	<0.001
Acute phase reactant elevation/Peripheral lap-lung nodule	23.803	0.087

Discussion

In our study, it was observed that the patient group in which latent TB screening was performed most frequently in internal medicine and rheumatology included those patients with rheumatologic diseases before biological agent treatment. In addition, IGST was requested by patients with constitutional symptoms, elevated acute phase reactants, peripheral LAP, and lung nodules, to obtain results quickly and to exclude TB or to support the diagnosis, since M. tuberculosis is a slow-growing bacterium (approximately six weeks to grow in culture). IGST results were evaluated in detail.

Anti-TNF alpha agents, one of the biologic DMARDs (disease modifying drugs), are widely used in rheumatology. TNF cytokine plays an important role in the immune response against mycobacteria by stimulating macrophages and increasing the release of various cytokines and chemokines [9]. It makes an important contribution to the killing of mycobacteria within the cell and to the maintenance of granulomas. Disruption of the TNF response with anti-TNF drugs disturbs granuloma formation and maintenance, leading to the proliferation of Mycobacterium tuberculosis [10,11]. As a matter of fact, with the increase in the use of these drugs, there has been a significant increase in TB infection. Long-term follow-up studies of individuals receiving treatment have shown an increased incidence of TB compared to the general population [12].

Therefore, latent TB screening is recommended by both national and international associations before starting this drug group [13,14]. Although there is no clear consensus as to whether TST or IGST should be used for latent TB screening or whether both should be used together, studies have shown that IGST is more effective [15]. Guozhong Zhou, et al. conducted a meta-analysis comparing the predictive values between IGST and TST, which indicated that IGST is two times more effective than TST in detecting latent TB infection and predicting progression to active disease [16]. Nazlıgül. et al. also found that IGST was a better method than TST as a latent TB screening method in 47 patients with chronic inflammatory arthritis [17]. In addition, in our clinical practice, IGST was used for latent TB screening before biological agent treatment in accordance with the literature.

In a study by Lee et al. [18], 342 patients underwent TST and IGST before biological agents, and the decision for TB prophylaxis was based on the results of IGST. IGST positivity in these patients was found to be approximately 30%. All patients with positive IGST results received TB prophylaxis. After a mean follow-up period of 41.7 months, five patients developed active TB. Of these patients, four were initially IGST negative, and one was initially IGST positive and developed active TB despite receiving TB prophylaxis. In our study, IGST was requested by 266 patients before biological agents, and positive results were found in 80 patients (30.14%). Active infection developed in three patients receiving biologic agent treatment, and one of these patients developed active disease after completing INH prophylaxis. The mean duration of biological agent use in patients with active TB was 35.73 months. The findings in the current study were similar to those in the literature.

In studies examining the data of patients using biological agents in countries such as France, England, and Spain, it was reported that TB infections developing after anti-TNF agents were mostly extrapulmonary. The same data showed

that patients using adalimumab and infliximab had a higher risk of developing TB than those using etanercept [12,19,20]. In our study, IGST positivity was higher in patients using adalimumab and infliximab than in patients using other biologic agents. Patients who developed active TB were those on adalimumab and sertolizumab. In our study, all of the active TB infections that developed due to the use of biological agents were pulmonary tuberculosis, unlike the literature. This may be explained by the low number of patients with active TB infection.

IGST positivity is not an indicator of whether the patient has an active infection. A positive test indicates whether the person has had previous exposure to TB bacilli. However, since it takes up to six weeks for TB bacilli to grow in cell culture, this test can sometimes be used to support clinical and radiologic diagnosis in patients with TB symptoms and to start treatment rapidly, or conversely, to exclude TB infection. In a study by Caliskan et al. [5], IGST was performed in 51 patients with suspected TB and positivity was observed in 12 patients (24%). Of these patients, four (33.3%) were found to have active TB infection. Similarly, in our study, IGST was requested from 89 patients with suspected TB, and positivity was observed in 27 patients (30%). Active TB was observed in seven (25.9%) of the positive patients.

The most common symptoms of patients with active TB infection include high fever, coughing, and night sweats. In addition, TB-specific nodules, cavitary lesions, and peripheral LAPs can be seen in the lung. Kurt et al. evaluated 38 patients with active TB infection and found constitutional symptoms, such as fever in 82%, night sweats in 48%, and anorexia in 20% of these patients. In addition, LAP was present in 57% of the patients [21]. Gülbay Eriş et al. [22] evaluated patients with active pulmonary TB and found that 35.9% had fever and 45% had night sweats. In our patient group, in accordance with the literature, TB was considered as a preliminary diagnosis in patients with constitutional symptoms, such as night sweats, anorexia, fever. Peripheral LAP and IGST were requested to support or rule out the diagnosis.

Limitation

The most important limitation of our study is that it is retrospective, and screening for tuberculosis was done only with the interferon gamma release test. There is a need for multi-center, prospective studies with large patient participation in this regard.

Conclusion

In summary, IGST is the most common internal medicine and rheumatology clinic screening used for latent TB infection prior to the use of biologic agents and JAK inhibitors. If active TB is not detected in positive cases, it is requested to prevent activation by giving prophylaxis. In the current study, it was observed that 38 patients with IGST positivity had previously used biological agents and JAK2 inhibitors for an average of 42.3 months. It was concluded that IGST positivity was seen more frequently in patients using adalimumab and certolizumab than in patients using other biologic agents and JAK2 inhibitors. In addition, especially in internal medicine, TB infection appears in patients with unexplained acute phase reactant elevation, in patients with constitutional symptoms and in patients with Lung nodules/hilar LAP. In patients with these symptoms, it was concluded that IGST was requested by the clinician to quickly rule out TB or to exclude its diagnosis, since TB bacillus is a bacterium whose growth is delayed.

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